



UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kai LICHIA et al.

Examiner: KOSAR, Andrew D.

Serial No.: 10/762,582

Group Art Unit: 1654

Filed: January 23, 2004

Title: HYDROPHILIC, THIOL-REACTIVE CYANINE DYES AND CONJUGATES
THEREOF WITH BIOMOLECULES FOR FLUORESCENCE DIAGNOSIS

APPEAL BRIEF

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on November 28, 2006, please consider the following.

The attached check includes the fee as set forth under § 41.20(b)(2).

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is Schering AG.

(ii) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(iii) STATUS OF CLAIMS

Claims 1-25, 33 and 35-41 are pending in the present application.

Claims 26-32 and 34 were cancelled.

Claims 2, 3, 5, 8, 11, 14-17, 20-25, 33 and 36-39 were withdrawn from consideration.

Claims 6, 7, 9, 10, 12, 13 and 40 were allowed.

03/29/2007 AWONDAF1 00000046 10762582

Claims 1, 4, 18, 19, 35 and 41 were rejected.

02 FC:1402

500.00 0P

Claims 1, 4, 18, 19, 35 and 41 are on appeal.

(iv) STATUS OF AMENDMENTS

An amendment was filed concurrently with the filing of the present Appeal Brief. Applicants assume for purposes herein that the amendment will be entered since it merely corrects the obviously incorrect dependency of claim 41, which was pointed out by the Examiner.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' appealed invention is directed to indotricarbocyanine dyes of formula (I), see structure thereof in claim 1, for example, (see page 4, last paragraph on said page, to about the last 6 lines of page 5, of the specification), and to solvates thereof (see page 5, line 7 from the bottom of the page, of the specification).

The appealed invention is furthermore directed to solvates of to indotricarbocyanine dyes of formulae II, III, V, VI, VIII and IX, see structures thereof in claim 40, for example, (see pages 8-10 and page 5, line 7 from the bottom of the page, of the specification).

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds for rejections are:

- (1) the rejection under 35 U.S.C. § 103, i.e., whether claims 1, 4, 18 and 19 are unpatentable over Flanagan in view of Achilefu, Alfheim, Miwa, Chorev, Zaheer, Rosenblatt, and Brown.
- (2) the rejections under 35 U.S.C. § 112, first paragraph, i.e., whether claims 35 and 41 are enabled.

(vii) ARGUMENT

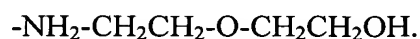
The Rejections Under 35 USC 103:

The rejection is set out in the Final Rejection mailed on July 28, 2006, and the Office Action mailed on December 30, 2005.

The rejection is over the combination of eight (8) references, where the Office Action takes parts of various compounds, e.g., certain groups present in various compounds, from different references, and combines them, e.g., places them on compounds of other reference(s), to yield applicant's claimed compounds.

Such combination of various parts of different compounds is not a proper basis for an obviousness rejection under strong Federal Circuit precedent such as *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992) and *In re Baird*, 16 F.2d 380, 29 U.S.P.Q. 2d 1550 (Fed. Cir. 1994).

Note in this regard, particularly, the analysis used by the Court in *Jones*. The group at issue in *Jones* had the structure



The PTO tried to rely on the single reference's compound having two CH₂CH₂OH groups attached to a single N atom, instead of linked together as shown above. The Court stated that one could not ignore the fact that the two CH₂CH₂OH groups were not joined together to form the ether linkage-containing group required in the claim. One could not simply rely on the "-CH₂CH₂O-" features of the reference; one had to consider the entirety of the structure involved. The Patent and Trademark Office also tried to rely on a morpholino group in the single reference wherein the nitrogen atom has two ethyl groups bonded to it and linked to each other by a single oxygen atom, thereby allegedly providing the "missing" ether oxygen noted above. Again, the Court stated that one could not ignore the entirety of the structure, i.e., the fact that this prior art group compound was cyclic. One could not apply components of its structural features in isolation apart from the group's overall structure. Other similar analyses were rejected by the Court.

For sake of simplicity, the discussion in large part focuses on the disclosure of two of the eight references.

Likewise here to the situation in *Jones*, the disclosure of WO '810, for example, that an increase in the number of sulfonic acid groups resulted in a reduction of toxicity cannot be separated from the specific compounds taught by WO '810. Analogously, the teaching in Chorev, for example, that maleimido forms a stable thio-ether bond cannot be separated from the specific compounds taught by Chorev. Such piecing together of an invention from various differing structures from different references is improper under well settled precedents. For example, no teaching or motivation is provided in WO '810, that there is a need or desire to form stable thio-ether bonds with the compounds of WO '801. Additionally, nothing in WO '810 teaches where such thio-ether bonds would be desired on the compounds taught therein and/or how such bonds could be achieved. Likewise, nothing in Chorev teaches how a reduction in toxicity can be achieved, or where, for example, sulfonic acid groups of WO '810 should be placed, or how such combination could be

achieved. Moreover, it is entirely unclear from the references that even if such piecing together would be performed, whether the resultant compounds would have the desired properties. One of ordinary skill in the art would not have an expectation of success based on the teachings of the prior art to prepare compounds with the desired properties.

Thus, a teaching that a certain substituent for a certain disclosed compound lowers its toxicity, and a further teaching that another substituent on a different compound renders such compound more stable, and so on (see full list of allegations in the rejection), do not create motivation to employ these various substituents on any position of any other particular compound. Disclosure of particular generic formulae and/or species with their particular set of structural components, under *Baird* and *Jones*, does not motivate one of ordinary skill in the art to select various structural features from different compounds or from different generic formulae in isolation and apply them to other compounds or other generic formulae.

Moreover, without appellants' own disclosure as a roadmap to piecing together the claimed invention herein, one of ordinary skill in the art would not have ended up with appellants' invention based on the disclosure of the various references. Not one single reference generically teaches each and every component of the claimed invention herein and/or even how the pieces of the various compounds should be formulated into a single structure. Moreover, there is no motivation in the references for the particular combinations alleged. For example, the compounds of WO '810 and Chorev have nothing to do with each other. WO '810 teaches near infrared fluorescent contrast agents (see title) of compounds of formula I therein disclosed on page 3, for example. Compare this to Chorev's thiol-reactive maleimido-based radiolabeling reagents (see title) of formula I therein on column 2, for example. Both the uses of the compounds of the two references are different, and the structures of the disclosed compounds of the two references are not similar. Without the disclosure of the present application, one of ordinary skill in the art would not know how pieces of the compounds of these references could be pieced together. Moreover, Chorev would not even be considered because it is non-analogous art, relating to a different field and problem.

There is no motivation justifiable under controlling precedent that would allow the holding of obviousness of a compound based on the piecing together of said compound from various unrelated compounds of different references.

In the Final Rejection the Examiner distinguishes the present case from *Jones*, and states that

Jones compares two compounds ... and the issue is connectivity of atoms within a single structure, and the non-obviousness to rearrange the atoms, and not the reliance upon secondary references to bring in the missing elements. Here the compounds of the prior art are highly analogous, sharing a significant core structure, where any one reference could be relied upon as the primary reference.

Applicants submit that the motivation to “rearrange” elements or groups within a single compound, which was not allowed to stand in support of an obviousness rejection in *Jones*, would more likely occur to one of ordinary skill in the art than the selection of elements or various groups from various references, e.g., 8 references, and rearrange such elements or groups to achieve a specific structure. For example, one of ordinary skill in the art would not first have to find a motivation to select the various references from among many prior art references, as one reference would contain all that is needed to make selections for the rearrangement.

Additionally, the allegation that the compounds combined share a significant core structure is incorrect. A comparison of the structures of the compounds of WO ‘810 and Chorev readily illustrates the lack of a common significant core structure. The compounds of WO ‘810 contain two multi-cyclic structures connected by a bridging group. See, for example, pages 3 of the reference. Various examples in WO ‘810 of these multi-cyclic groups, which can be substituted with various groups, are easily seen in the multitude of species depicted throughout the disclosure as well as the nature of the bridging group, which can be straight chain (see compounds on page 54, for example) or can contain various cyclic structures with side chains further containing cyclic structures (see compounds on page 61, for example). The compounds of Chorev contain two single cyclic groups, one being a single phenyl ring with a hydroxy group attached and an R² group which is a radionuclide, e.g., ¹²²I, ⁷⁷Br, etc., (see claim 1 of Chorev, for example) and this phenyl ring is connected by a bridging group to a second single cyclic group. Neither cyclic group in Chorev’s compounds even remotely resembles either cyclic group in WO ‘810’s compounds. Additionally, the respective bridging groups of these references also do not appear to overlap in structure. Thus, the allegation that the compounds of the various references share a significant core structure is incorrect. These compounds have nothing in common other than that they are both compounds made up of various atoms, e.g., carbon, nitrogen, etc.

Moreover, once the combination is extended to require eight different references as alleged, each contributing something to the alleged combination, the rejection becomes even more untenable.

For all the foregoing reasons, the claims are not obvious.

The Rejections Under 35 USC 112:

The Final Rejection cites Vipagunta teaching allegedly that generally the prediction of the formation of solvates is complex and difficult, and that the result may be an unstable system, that various types of phase changes are possible, and that such may affect bioavailability, etc. Based on such teachings, the Final Rejection alleges that the art has high unpredictability with regards to solvates and that one would be burdened with undue experimentation to make solvates.

Even assuming that all the general allegations regarding the teachings of Vipagunta are correct, there is no basis for the rejection.

First and foremost, a specification disclosure which “contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra*.

The Examiner has not established any basis to doubt objective enablement. There is no indication that one of ordinary skill in the art would have questioned that solvates could be formed in view of the disclosure and the state of the art. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (CA FC 2005).

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. “The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation.” *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art

merely through routine laboratory efforts can take various compounds of the invention, which are enabled, bring them together with various solvents under various conditions and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Any amount of instability, phase changes, etc., can be determined by routine testing. As discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the “test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.”

The Examiner also alleges that the bioavailability of the solvates may be different than those of the compounds themselves. However, such has no relation to whether such solvates are enabled or not.

Reversal of the rejections is respectfully and courteously requested.

Respectfully submitted,



Csaba Henter (Reg. No. P-50,908)
Anthony J. Zelano (Reg. No. 27,969)
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

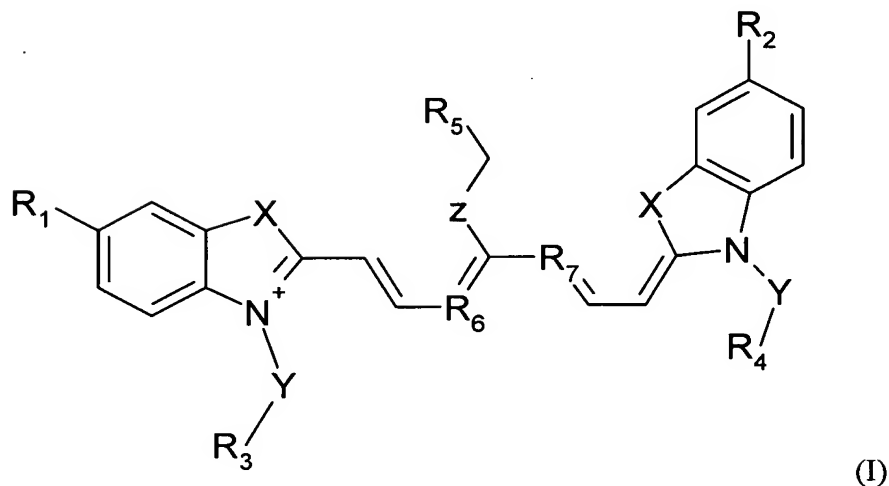
Attorney Docket No.: SCH-2208

Date: **March 28, 2007**

CH/AJZ/pdrK:\Sch\2208\Appeal Brief.doc

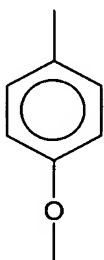
(viii) CLAIMS APPENDIX

1. An indotricarbocyanine dye of formula (I),



in which

- X is O, S or C, wherein, when X is C, it is substituted twice by methyl, ethyl, propyl, isopropyl and/or butyl,
- Y is CH₂-CH₂ or CH₂-CH₂-CH₂,
- Z is C₁ to C₅ alkyl, wherein one or more C atoms are optionally replaced by O or S, or is



which is bound by an ethylene or a methylene bridge to

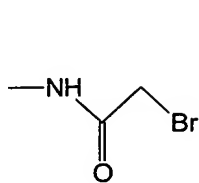
R₅,

R₁ to R₄ are, independently of one another, SO₃H or H, with the proviso that at least three of R₁ to R₄ are SO₃H,

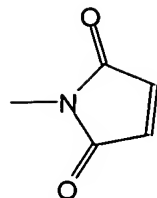
R₅ is COOH, NH₂, -CO-NH-R₈-R₉, -NH-CS-NH-R₈-R₉ or -NH-CO-R₈-R₉,
in which R₈ is an unbranched C₂-C₁₃ alkyl, in which C atoms are optionally

replaced by O or S,

R₉ is



or



or chloroacetyl,

bromoacetyl, iodoacetyl, chloroacetamido, iodoacetamido, chloroalkyl,

bromoalkyl, iodoalkyl, pyridyl disulfide or vinyl sulfonamide,

R₆ and R₇ are CH or are connected together by a C₃-alkylene group to form a cyclohexyl,

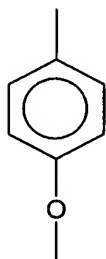
which optionally can be substituted in para-position with a C₁ to C₄-alkyl

radical,

or a salt thereof.

4. An indotricarbocyanine dye according to claim 1, in which

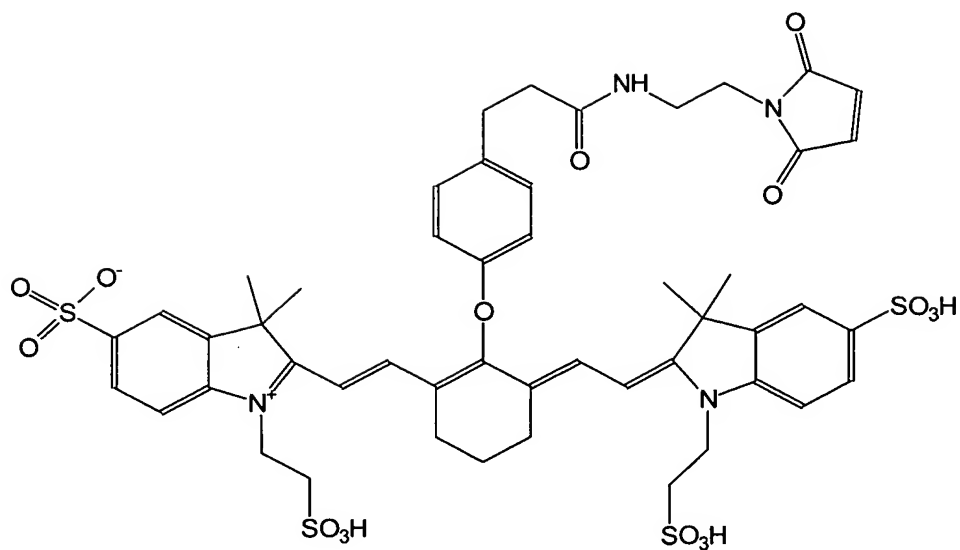
Z is



which is bound by an ethylene or a methylene bridge to R₅,

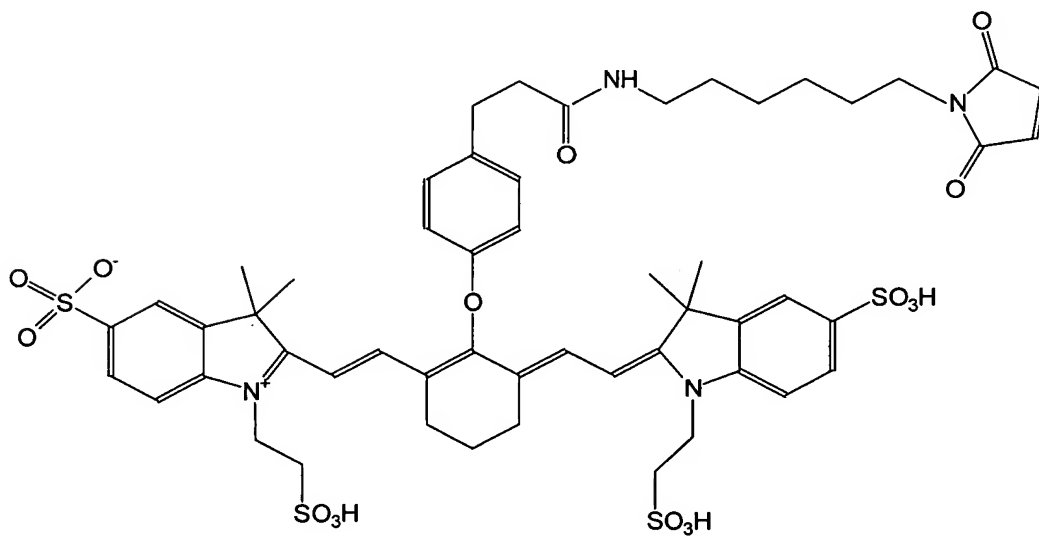
and R₆ and R₇ are connected together by a C₃-alkylene group to form a cyclohexyl.

18. An indotricarbocyanine dye according to claim 4 of formula (XIV)



or a salt thereof.

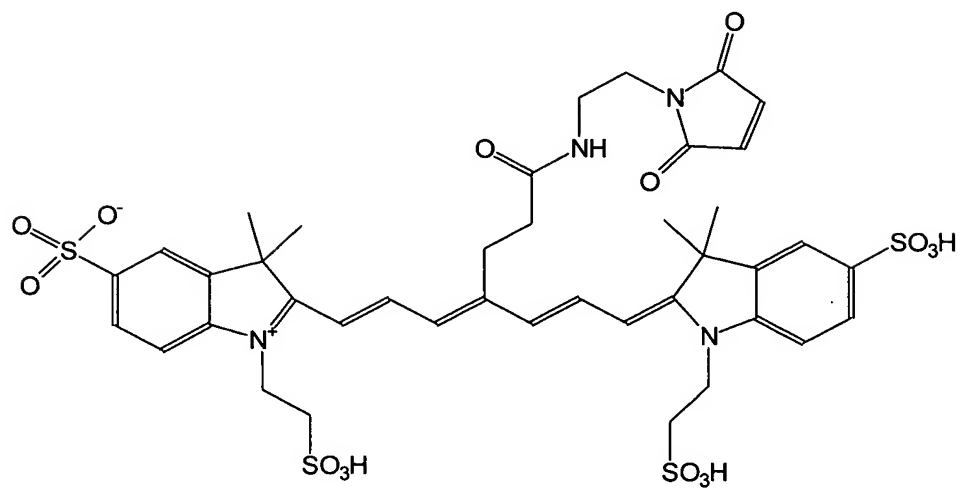
19. An indotricarbocyanine dye according to claim 4 of formula (XV)



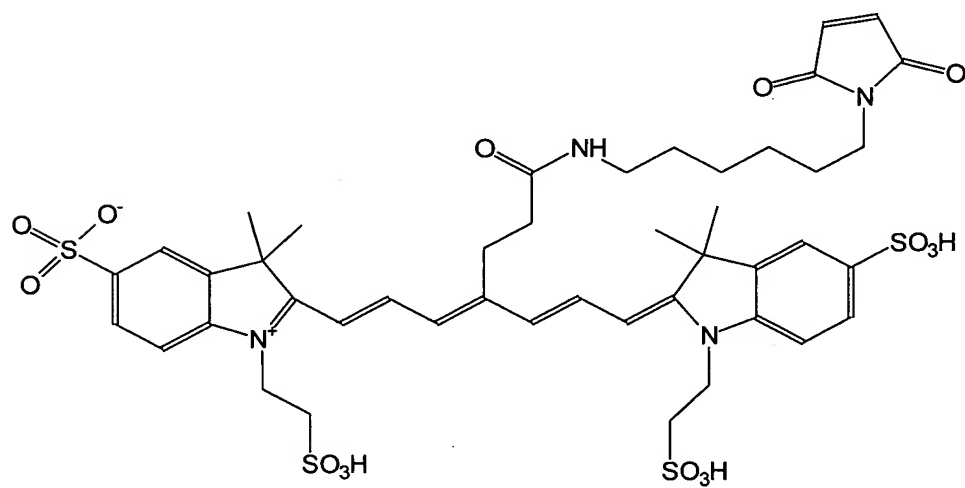
or a salt thereof.

35. A solvate of a compound of claim 1, which comprises a compound of formula I in combination with a solvent molecule.

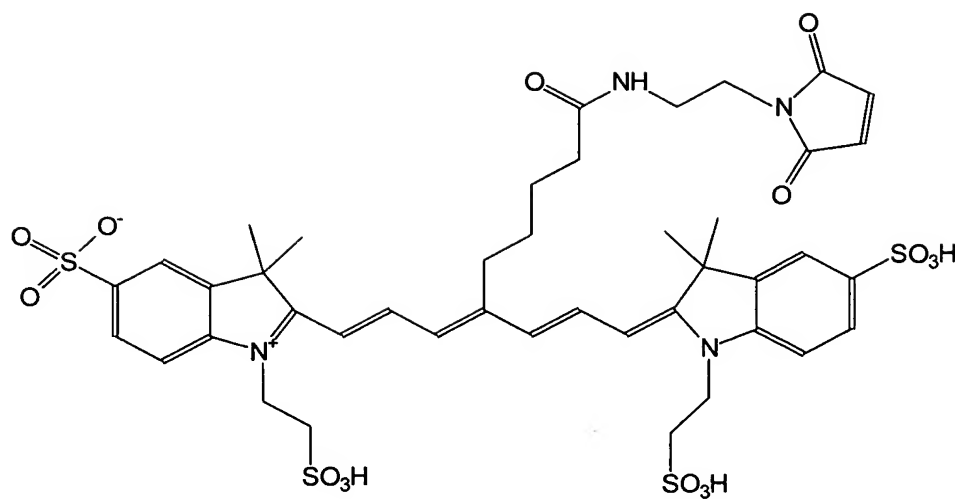
40. An indotricarbocyanine dye of formula (II)



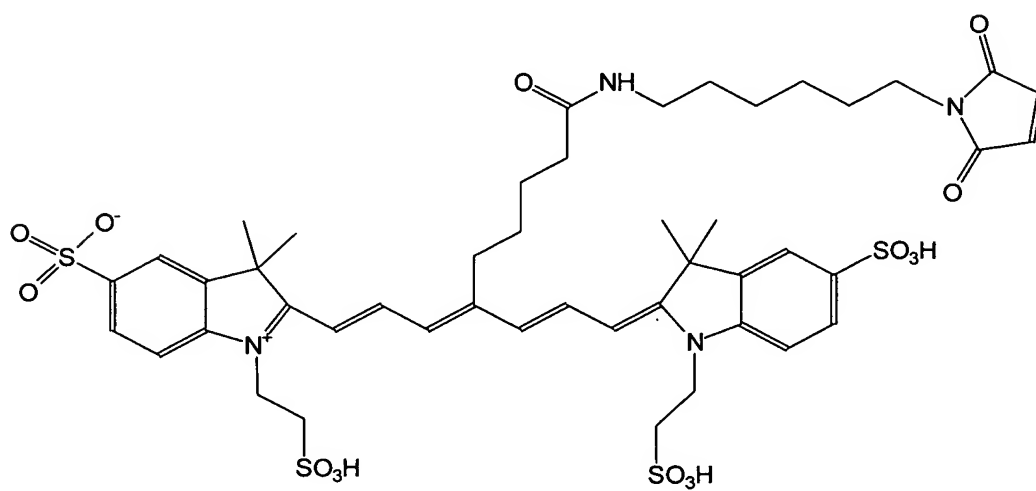
or of formula (III)



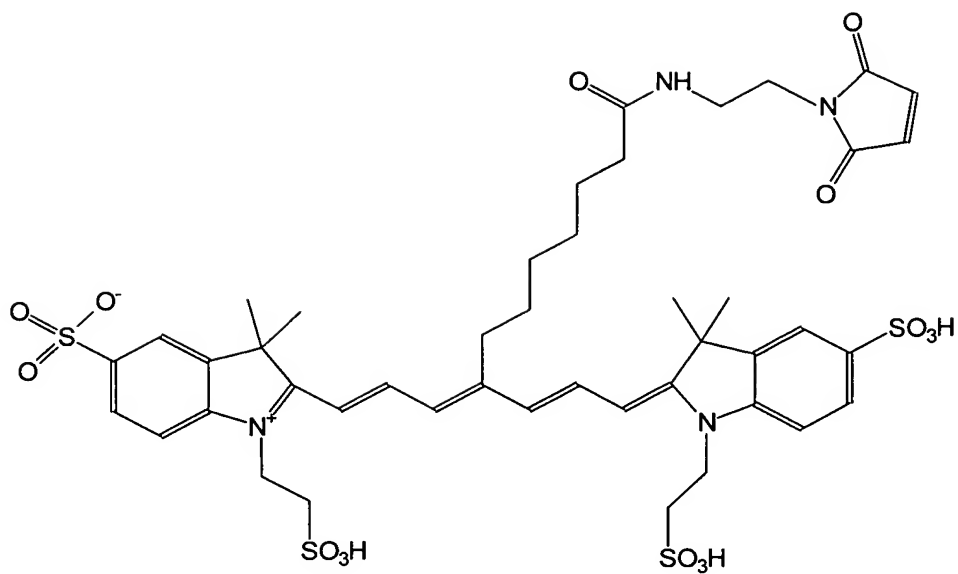
or of formula (V)



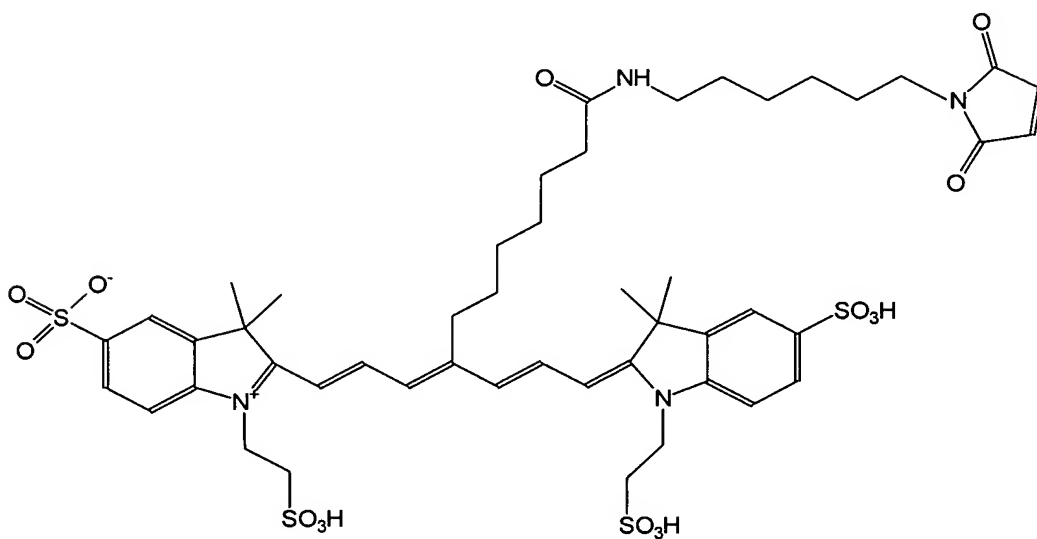
or of formula (VI)



or of formula (VIII)



or of formula (IX)



or a salt thereof.

41. A solvate of a compound of claim 40, which comprises a compound of formula II, III, V, VI, VIII or IX in combination with a solvent molecule.

(ix) EVIDENCE APPENDIX

None

(x) RELATED PROCEEDINGS APPENDIX

None